229

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NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	FEB 27	New STN AnaVist pricing effective March 1, 2006
NEWS	4	APR 04	STN AnaVist $500 visualization usage credit offered
NEWS	5	MAY 10	CA/CAplus enhanced with 1900-1906 U.S. patent records
NEWS	6	MAY 11	KOREAPAT updates resume
NEWS	7	MAY 19	Derwent World Patents Index to be reloaded and enhanced
NEWS	8	MAY 30	IPC 8 Rolled-up Core codes added to CA/CAplus and USPATFULL/USPAT2
NEWS	9	MAY 30	The F-Term thesaurus is now available in CA/CAplus
NEWS	10	JUN 02	The first reclassification of IPC codes now complete in INPADOC
NEWS	11	JUN 26	TULSA/TULSA2 reloaded and enhanced with new search and and display fields
NEWS	12	JUN 28	Price changes in full-text patent databases EPFULL and PCTFULL
NEWS	13	JUl 11	CHEMSAFE reloaded and enhanced
NEWS	14	JUl 14	FSTA enhanced with Japanese patents
NEWS	15	JUl 19	Coverage of Research Disclosure reinstated in DWPI

NEWS EXPRESS JUNE 30 CURRENT WINDOWS VERSION IS V8.01b, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8
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FILE 'HOME' ENTERED AT 12:51:24 ON 24 JUL 2006

=> FIL CAPLUS

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

229

FILE 'CAPLUS' ENTERED AT 12:51:43 ON 24 JUL 2006
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FILE COVERS 1907 - 24 Jul 2006 VOL 145 ISS 5
FILE LAST UPDATED: 23 Jul 2006 (20060723/ED)

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E25         1     258285-15-3/BI

=> S E3
L1          1 258284-99-0/BI

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THE ESTIMATED COST FOR THIS REQUEST IS 2.74 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L1   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:        2000:30387  CAPLUS
DOCUMENT NUMBER:         132:151895
TITLE:                   Synthesis of α-substituted aminocarboxylic acids
```

229

AUTHOR(S): Saratovskikh, I. V.; Kalashnikov, V. V.; Ragulin, V. V.
CORPORATE SOURCE: Institute of Physiologically Active Substances, Russian Academy of Sciences, Chernogolovka, Russia
SOURCE: Russian Journal of General Chemistry (Translation of Zhurnal Obshchei Khimii) (1999), 69(7), 1173-1175
CODEN: RJGCEK; ISSN: 1070-3632
PUBLISHER: MAIK Nauka/Interperiodica Publishing
DOCUMENT TYPE: Journal
LANGUAGE: English
ABSTRACT:
Alkylation of Schiff bases of amino acids, PhCH:NCHRCO2R1 (R = Me, Ph, Me2CH, PhCH2; R1 = Me, Et) with R22P(O)(CH2)nBr (R2 = OEt, Ph; n = 2-5) followed by hydrolysis gave 32-85% 7 R32P(O)(CH2)nCR(NH2)CO2H (R3 = OH, Ph; R = same as above; n = 2-5).

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> DIS L1 1 IALL
THE ESTIMATED COST FOR THIS REQUEST IS 3.07 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L1 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:30387 CAPLUS
DOCUMENT NUMBER: 132:151895
ENTRY DATE: Entered STN: 13 Jan 2000
TITLE: Synthesis of α-substituted aminocarboxylic acids
AUTHOR(S): Saratovskikh, I. V.; Kalashnikov, V. V.; Ragulin, V. V.
CORPORATE SOURCE: Institute of Physiologically Active Substances, Russian Academy of Sciences, Chernogolovka, Russia
SOURCE: Russian Journal of General Chemistry (Translation of Zhurnal Obshchei Khimii) (1999), 69(7), 1173-1175
CODEN: RJGCEK; ISSN: 1070-3632
PUBLISHER: MAIK Nauka/Interperiodica Publishing
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 29-7 (Organometallic and Organometalloidal Compounds)
Section cross-reference(s): 34
ABSTRACT:
Alkylation of Schiff bases of amino acids, PhCH:NCHRCO2R1 (R = Me, Ph, Me2CH, PhCH2; R1 = Me, Et) with R22P(O)(CH2)nBr (R2 = OEt, Ph; n = 2-5) followed by hydrolysis gave 32-85% 7 R32P(O)(CH2)nCR(NH2)CO2H (R3 = OH, Ph; R = same as above; n = 2-5).

SUPPL. TERM: phosphorylalkyl amino acid prepn
INDEX TERM: 1186-10-3, Diethyl 3-bromopropylphosphonate 5055-14-1
5324-30-1, Diethyl 2-bromoethylphosphonate 40216-61-3
40216-77-1 42757-42-6, Diethyl 5-bromopentylphosphonate
60855-77-8 63075-66-1, Diethyl 4-bromobutylphosphonate
68906-71-8
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation of phosphorylalkyl substituted amino acids)
INDEX TERM: 258285-03-9P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of phosphorylalkyl substituted amino acids)
INDEX TERM: 157381-42-5P 258284-97-8P 258284-98-9P
258284-99-0P 258285-00-6P 258285-01-7P
258285-02-8P

ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation of phosphorylalkyl substituted amino acids)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD.
REFERENCE(S): (1) Evans, R; Br J Pharmacol 1982, V75(1), P65 CAPLUS
(2) Ragulin, V; US 1410489 Byull Izobret 1986
(3) Ragulin, V; Byull Izobret 1990, 34
(4) Ragulin, V; Ref Zh Khim 1991, 3N169P
(5) Salt, T; Neuroscience 1995, V65(1), P5 CAPLUS
(6) Tsvetkov, E; Russ J Gen Chem 1995, V65(9), P1300

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E22          3     170984-82-4/BI
E23          3     170984-82-4P/BI
E24          1     170984-85-7/BI
E25          1     170984-85-7P/BI

=> S E3
L2           1 170984-73-3/BI

=> DIS L2 1 IALL
THE ESTIMATED COST FOR THIS REQUEST IS 3.07 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L2   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:        1995:957967  CAPLUS
DOCUMENT NUMBER:         124:30404
ENTRY DATE:              Entered STN:  02 Dec 1995
TITLE:                   Preparation of α-tetrasubstituted-α-amino
                         acids as central nervous system agents.
INVENTOR(S):             Watkins, Jeffrey Clifton; Jane, David Edward
PATENT ASSIGNEE(S):      University of Bristol, UK; Tocris Cookson Ltd.
SOURCE:                  PCT Int. Appl., 40 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
INT. PATENT CLASSIF.:
           MAIN:         C07C229-24
    SECONDARY:           C07F009-38; C07F009-09; C07F009-30; A61K031-195;
                         A61K031-66
```

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CLASSIFICATION: 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9515940	A1	19950615	WO 1994-GB2690	19941209
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9512469	A1	19950627	AU 1995-12469	19941209
EP 733036	A1	19960925	EP 1995-903410	19941209
R: CH, DE, FR, GB, IT, LI, NL				

PRIORITY APPLN. INFO.: GB 1993-25368 A 19931210
WO 1994-GB2690 W 19941209

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9515940	ICM	C07C229-24
	ICS	C07F009-38; C07F009-09; C07F009-30; A61K031-195; A61K031-66
	IPCI	C07C0229-24 [ICM,6]; C07C0229-00 [ICM,6,C*]; C07F0009-38 [ICS,6]; C07F0009-09 [ICS,6]; C07F0009-30 [ICS,6]; C07F0009-00 [ICS,6,C*]; A61K0031-195 [ICS,6]; A61K0031-185 [ICS,6,C*]; A61K0031-66 [ICS,6]
	IPCR	C07C0229-00 [I,C*]; C07C0229-24 [I,A]; C07C0229-46 [I,A]; C07C0309-00 [I,C*]; C07C0309-61 [I,A]; C07F0009-00 [I,C*]; C07F0009-09 [I,A]; C07F0009-30 [I,A]; C07F0009-38 [I,A]
AU 9512469	IPCI	C07C0229-24 [ICM,6]; C07C0229-00 [ICM,6,C*]; C07F0009-38 [ICS,6]; C07F0009-09 [ICS,6]; C07F0009-30 [ICS,6]; C07F0009-00 [ICS,6,C*]; A61K0031-195 [ICS,6]; A61K0031-185 [ICS,6,C*]; A61K0031-66 [ICS,6]
	IPCR	C07C0229-00 [I,C*]; C07C0229-24 [I,A]; C07C0229-46 [I,A]; C07C0309-00 [I,C*]; C07C0309-61 [I,A]; C07F0009-00 [I,C*]; C07F0009-09 [I,A]; C07F0009-30 [I,A]; C07F0009-38 [I,A]
EP 733036	IPCI	C07C0229-24 [ICM,6]; C07C0229-00 [ICM,6,C*]; C07F0009-38 [ICS,6]; C07F0009-09 [ICS,6]; C07F0009-30 [ICS,6]; C07F0009-00 [ICS,6,C*]; A61K0031-195 [ICS,6]; A61K0031-185 [ICS,6,C*]; A61K0031-66 [ICS,6]

OTHER SOURCE(S): CASREACT 124:30404; MARPAT 124:30404
ABSTRACT:
R11R12NC(Q)(BY)(R10) [Y = carboxy, phosphono, PO2H(OR13), phosphinco, PO2H(R13), OPO3H2, OPO2(OR13), arsono, AsO2H(OR13), arsenico, AsO2H(R13), sulfo, sulfino, sulpheno, OSO3H, tetrazolyl, 3-hydroxyisoxazolyl, 1,2,4-oxadiazolidin-3,5-dione residue, hydantoin residue; R13 = alkyl, alkenyl, alkynyl, cycloalkyl, (substituted) aryl, aralkyl; B = (substituted) alkylene, cycloalkylene, alkenylene,alkynylene; Q = carboxy, alkoxycarbonyl, hydroxamic acid residue; R10 = alkyl, alkenyl, alkynyl, cycloalkyl, haloalkyl, (substituted) aryl, aralkyl, biaryl; R11, R12 = H, alkyl, alkenyl, alkynyl, acyl, (substituted) PhCO; 2 of Y, Q, R10, R11, R12 and the substituents on B being optionally condensed with each other to form a carbocyclic or heterocyclic ring system], were prepared Thus, (2R,5SR)-(-)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methylpyrazine in THF at -78° was treated with BuLi and then Me 4-bromobut-2-enoate in THF to give an oil which was treated successively with CF3CO2H and refluxing aqueous HCl to give 38.7%

(2S,1'S,2'S)-2-amino-2-(2'-carboxycycloprop-1'-yl)propanoic acid. Certain title compds. antagonize the ability of L-2-amino-4-phosphonobutyrate to depress forskolin-stimulated cAMP production in rat cerebral cortical tissue; they are said to be more potent and/or selective agonists or antagonists at metabotropic glutamate receptors.

SUPPL. TERM: excitatory amino acid agonist antagonist
INDEX TERM: Nervous system agents
(preparation of α-tetrasubstituted-α-amino acids as central nervous system agents)
INDEX TERM: Amino acids, preparation
ROLE: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of α-tetrasubstituted-α-amino acids as central nervous system agents)
INDEX TERM: Amino acids, biological studies
ROLE: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(excitatory, agonists and/or antagonists; preparation of α-tetrasubstituted-α-amino acids as central nervous system agents)
INDEX TERM: 3716-48-1P 66515-29-5P 102394-08-1P 104739-22-2P
157141-16-7P 157381-42-5P 170984-66-4P 170984-67-5P
170984-68-6P 170984-69-7P 170984-70-0P 170984-71-1P
170984-72-2P 170984-73-3P 170984-74-4P
170984-75-5P 171228-34-5P 171228-35-6P 171483-43-5P
ROLE: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of α-tetrasubstituted-α-amino acids as central nervous system agents)
INDEX TERM: 106-93-4, 1,2-Dibromoethane 1117-71-1, Methyl 4-bromobut-2-enoate 1638-86-4, Diethyl phenylphosphonite 2524-64-3, Diphenyl chlorophosphate 5324-30-1, Diethyl 2-bromoethylphosphonate 5332-06-9, 4-Bromobutanenitrile 5454-83-1, Methyl 5-bromopentanoate 64840-18-2 110117-71-0 132153-50-5
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation of α-tetrasubstituted-α-amino acids as central nervous system agents)
INDEX TERM: 170984-76-6P 170984-77-7P 170984-78-8P 170984-79-9P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of α-tetrasubstituted-α-amino acids as central nervous system agents)

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THE ESTIMATED COST FOR THIS REQUEST IS 3.07 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1985:178450 CAPLUS
DOCUMENT NUMBER: 102:178450
ENTRY DATE: Entered STN: 18 May 1985
TITLE: Gas chromatographic separation of enantiomeric sulfur compounds on Chirasil-Val
AUTHOR(S): Bayer, Ernst; Kuesters, Ernst; Nicholson, Graeme J.; Frank, Hartmut
CORPORATE SOURCE: Inst. Org. Chem., Univ. Tuebingen, Tuebingen, D-7400/1, Fed. Rep. Ger.
SOURCE: Journal of Chromatography (1985), 320(2), 393-6
CODEN: JOCRAM; ISSN: 0021-9673
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 80-4 (Organic Analytical Chemistry)
ABSTRACT:
The gas chromatog. separation of sulfoxide antipodes, including aliphatic sulfoxides,
on quartz fused silica capillaries coated with the chiral silicone phase Chirasil-Val is reported. The compds. were esterified before anal. A flame ionization detector and H carrier gas were used.

SUPPL. TERM: sulfoxide enantiomer gas chromatog; sulfur compd enantiomer gas chromatog
INDEX TERM: Chromatography, gas
(for resolution of enantiomeric sulfur compds. on Chirasil-Val)
INDEX TERM: Resolution
(of sulfur compound enantiomers by gas chromatog. on Chirasil-Val)
INDEX TERM: Sulfoxides
ROLE: ANST (Analytical study)
(resolution of enantiomeric, gas chromatog.)
INDEX TERM: 4170-69-8 33577-16-1 95833-61-7 95833-62-8
ROLE: ANST (Analytical study); PROC (Process)
(resolution of, by gas chromatog. on Chirasil-Val)
INDEX TERM: 3226-66-2 7314-32-1 23631-84-7 34044-66-1 41486-92-4
50896-97-4 50896-98-5 80225-50-9 95833-63-9
95833-64-0 95833-65-1 95833-66-2 95833-67-3

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95833-68-4 95833-69-5 95833-70-8 95833-71-9
95833-72-0 95833-73-1 95833-74-2
ROLE: ANST (Analytical study); PROC (Process)
(separation of, by gas chromatog. on Chirasil-Val)

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L4            4 66735-68-0/BI

=> DIS L4 1 IALL
THE ESTIMATED COST FOR THIS REQUEST IS 3.07 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L4   ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2004:452975  CAPLUS
DOCUMENT NUMBER:          141:12262
ENTRY DATE:               Entered STN:  04 Jun 2004
TITLE:                    Anti-microbial agents derived from methionine
                          sulfoximine analogues and use for treating
                          mycobacterial infections
INVENTOR(S):              Harth, Gunter; Griffith, Owen W.; Horwitz, Marcus A.
PATENT ASSIGNEE(S):       Regents of the University of California, USA
SOURCE:                   PCT Int. Appl., 40 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
INT. PATENT CLASSIF.:
            MAIN:         A61K
CLASSIFICATION:           63-5 (Pharmaceuticals)
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.        DATE
     ---------------      ----   --------    --------------------   --------
     WO 2004045539         A2    20040603    WO 2003-US36705        20031117
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WO 2004045539	C2	20040805			
WO 2004045539	A3	20041111			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR					
AU 2003295579	A1	20040615	AU 2003-295579		20031117
US 2004157802	A1	20040812	US 2003-715679		20031117
US 2006142251	A1	20060629	US 2005-534660		20051128
PRIORITY APPLN. INFO.:			US 2002-426502P	P	20021115
			US 2002-430407P	P	20021202
			WO 2003-US36705	W	20031117

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004045539	ICM	A61K
	IPCI	A61K [ICM,7]
	IPCR	A61K0031-185 [I,C*]; A61K0031-196 [I,A]; A61K0031-34 [I,A]; A61K0031-34 [I,C*]; A61K0031-44 [I,A]; A61K0031-44 [I,C*]
	ECLA	A61K031/196; A61K031/34; A61K031/44; A61K031/196+M; A61K031/34+M; A61K031/375+M; A61K031/44+M
AU 2003295579	IPCI	A61K0031-195 [ICM,7]; A61K0031-185 [ICM,7,C*]; A61K0031-34 [ICS,7]; A61K0031-44 [ICS,7]
	IPCR	A61K0031-185 [I,C*]; A61K0031-196 [I,A]; A61K0031-34 [I,A]; A61K0031-34 [I,C*]; A61K0031-44 [I,A]; A61K0031-44 [I,C*]
US 2004157802	IPCI	A61K0031-66 [ICM,7]; A61K0031-185 [ICS,7]; A61K0031-198 [ICS,7]
	IPCR	A61K0031-185 [I,A]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]; A61K0031-66 [I,A]; A61K0031-66 [I,C*]
	NCL	514/114.000
US 2006142251	IPCI	A61K0031-198 [I,A]; A61K0031-185 [I,C*]; A61K0031-66 [I,A]
	NCL	514/114.000; 514/562.000

OTHER SOURCE(S): MARPAT 141:12262

ABSTRACT:
Novel antimicrobial compns. containing analogs of L-methionine-SR-sulfoximine (MSO) that are effective in treating intracellular pathogen infections are provided. Specifically, the compns. provided are MSO analogs having superior antimicrobial activity with significantly less toxicity as compared to MSO. These MSO analogs are suitable for use in treating infection in animals including primates, cows, pigs, horses, rabbits, mice, rats, cats, and dogs. Moreover, the MSO analogs are ideally suited for treating infections caused by the genus Mycobacterium. Addnl., methods for using the novel MSO analogs are also provided.

SUPPL. TERM: antimicrobial agent mycobacterium methionine sulfoximine analog

INDEX TERM: Bos taurus
Canis familiaris
Equus caballus
Felis catus
Human
Mammalia
Monkey
Mycobacterium avium
Mycobacterium bovis

Mycobacterium tuberculosis
Oryctolagus cuniculus
Rodentia
Sus scrofa domestica
(anti-microbial agents derived from methionine sulfoximine analogs and use for treating mycobacterial infections)

INDEX TERM: Antibacterial agents
(anti-mycobacterial; anti-microbial agents derived from methionine sulfoximine analogs and use for treating mycobacterial infections)

INDEX TERM: Infection
(bacterial, mycobacterial, treatment of; anti-microbial agents derived from methionine sulfoximine analogs and use for treating mycobacterial infections)

INDEX TERM: Mycobacterium
(infection, treatment of; anti-microbial agents derived from methionine sulfoximine analogs and use for treating mycobacterial infections)

INDEX TERM: 7732-18-5, Water, uses
ROLE: NUU (Other use, unclassified); USES (Uses)
(anti-microbial agents derived from methionine sulfoximine analogs and use for treating mycobacterial infections)

INDEX TERM: 74-93-1, Methane thiol, reactions 143-33-9, Sodium cyanide 1066-33-7, Ammonium bicarbonate 1629-58-9, Ethyl vinyl ketone 5925-75-7 26628-22-8, Sodium azide
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(anti-microbial agents derived from methionine sulfoximine analogs and use for treating mycobacterial infections)

INDEX TERM: 66735-71-5P, α-Ethyl-DL-methionine
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(anti-microbial agents derived from methionine sulfoximine analogs and use for treating mycobacterial infections)

INDEX TERM: 50-81-7, Ascorbic acid, biological studies 54-85-3, Isoniazid 1982-67-8D, Methionine sulfoximine, analogs 15985-39-4 66735-67-9 66735-68-0
ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-microbial agents derived from methionine sulfoximine analogs and use for treating mycobacterial infections)

INDEX TERM: 9023-70-5, Glutamine synthetase (
ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitor; anti-microbial agents derived from methionine sulfoximine analogs and use for treating mycobacterial infections)

=> DIS L4 2 IALL
THE ESTIMATED COST FOR THIS REQUEST IS 3.07 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L4 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1988:132274 CAPLUS
DOCUMENT NUMBER: 108:132274
ENTRY DATE: Entered STN: 15 Apr 1988
TITLE: Amino acid sulfoximines: α-ethylmethionine

sulfoximine
AUTHOR(S): Griffith, Owen W.
CORPORATE SOURCE: Med. Coll., Cornell Univ., New York, NY, 10021, USA
SOURCE: Methods in Enzymology (1987), 143(Sulfur Sulfur Amino Acids), 286-91
CODEN: MENZAU; ISSN: 0076-6879
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 34-2 (Amino Acids, Peptides, and Proteins)
ABSTRACT:
α-Ethylmethionine sulfoxime, HO2CCEt(NH2)CH2CH2S(O)Me:NH, was prepared by treatment of HO2CCEt(NH2)CH2CH2SMe (I) with HCl. I was prepared by treatment of EtCOCH:CH2 with MeSH to give EtCOCH2CH2SMe which was converted to a hydantoin derivative with (NH4)2CO3 and NaCN and the product hydrolyzed to I.

SUPPL. TERM: ethylmethionine sulfoximine
INDEX TERM: 66735-70-4P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrolysis of)
INDEX TERM: 66735-71-5P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction with hydrazoic acid)
INDEX TERM: 66735-68-0P 113350-10-0P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
INDEX TERM: 66735-69-1P, Ethyl 2-(methylthio)ethyl ketone
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation of and hydantoin derivative preparation from)
INDEX TERM: 74-93-1, Methanethiol, reactions
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with Et vinyl ketone)
INDEX TERM: 7782-79-8, Hydrazoic acid
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with ethylmethionine)
INDEX TERM: 1629-58-9, Ethyl vinyl ketone
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with methanethiol)

=> DIS L4 3 IALL
THE ESTIMATED COST FOR THIS REQUEST IS 3.07 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L4 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1979:198299 CAPLUS
DOCUMENT NUMBER: 90:198299
ENTRY DATE: Entered STN: 12 May 1984
TITLE: Inhibition of glutathione biosynthesis by prothionine sulfoximine (S-n-propyl homocysteine sulfoximine), a selective inhibitor of γ-glutamylcysteine synthetase
AUTHOR(S): Griffith, Owen W.; Anderson, Mary E.; Meister, Alton
CORPORATE SOURCE: Med. Coll., Cornell Univ., New York, NY, USA
SOURCE: Journal of Biological Chemistry (1979), 254(4), 1205-10
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 3-5 (Biochemical Interactions)
Section cross-reference(s): 7

ABSTRACT:
DL-Prothionine SR-sulfoximine [70085-86-8] and α-methyl-DL-prothionine-SR-sulfoximine [70056-05-2] were prepared and found to markedly inhibit γ-glutamylcysteine synthetase [9023-64-7] but to not significantly affect glutamine synthetase [9023-70-5]. After injection of prothionine sulfoximine into mice, the level of kidney glutathione [70-18-8] decreased rapidly to .apprx.20% of the control level indicating that a large fraction, rather than a small pool, of glutathione participates in rapid turnover. The rapid decline of the glutathione level that occurs after inhibition of glutathione synthesis reflects the normal rate of intracellular glutathione utilization by the γ-glutamyl cycle. A number of related sulfoximines were synthesized and tested as inhibitors of glutamine and γ-glutamylcysteine synthetases.

SUPPL. TERM: glutathione formation prothionine sulfoximine; glutamylcysteine synthetase prothionine sulfoximine

INDEX TERM: Kidney, metabolism
(glutathione formation by, prothionine sulfoximine inhibition of)

INDEX TERM: Molecular structure-biological activity relationship
(glutamylcysteine synthetase-inhibiting, of prothionine sulfoximine analogs)

INDEX TERM: 70-18-8, biological studies
ROLE: FORM (Formation, nonpreparative)
(formation of, by kidney, methionine sulfoximine inhibition of)

INDEX TERM: 15985-39-4 66735-67-9 66735-68-0
ROLE: PRP (Properties)
(glutamylcysteine synthetase inhibition by)

INDEX TERM: 9023-64-7
ROLE: PROC (Process)
(methionine sulfoximine inhibition of)

INDEX TERM: 15985-39-4P 70056-00-7P 70056-01-8P 70056-02-9P
70056-03-0P 70056-05-2P 70085-86-8P 70085-87-9P
ROLE: PREP (Preparation)
(preparation and glutamylcysteine synthetase-inhibiting activity of)

INDEX TERM: 44768-66-3P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation and hydantoinylation of)

INDEX TERM: 70085-85-7P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and saponification of)

INDEX TERM: 557-02-8P 2598-46-1P 2749-07-7P 16820-52-3P
16820-66-9P 42537-72-4P 70056-04-1P 70056-06-3P
70095-14-6P
ROLE: PREP (Preparation)
(preparation of)

INDEX TERM: 9023-70-5
ROLE: PRP (Properties)
(prothionine sulfoximine inhibition of glutamylcysteine synthetase in relation to)

INDEX TERM: 107-03-9
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with acrolein)

INDEX TERM: 107-02-8, biological studies
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with propanethiol)

INDEX TERM: 14109-74-1
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reductive amination of)

=> DIS L4 4 IALL
THE ESTIMATED COST FOR THIS REQUEST IS 3.07 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L4 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1978:500916 CAPLUS
DOCUMENT NUMBER: 89:100916
ENTRY DATE: Entered STN: 12 May 1984
TITLE: Differential inhibition of glutamine and γ-glutamylcysteine synthetases by α-alkyl analogs of methionine sulfoximine that induce convulsions
AUTHOR(S): Griffith, Owen W.; Meister, Alton
CORPORATE SOURCE: Dep. Biochem., Cornell Univ. Med. Coll., New York, NY, USA
SOURCE: Journal of Biological Chemistry (1978), 253(7), 2333-8
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 3-5 (Biochemical Interactions)
ABSTRACT:
α-Methyl-DL-methionine (SR)-sulfoximine [66735-67-9] and α-ethyl-DL-methionine (SR)-sulfoximine [66735-68-0], like L-methionine (SR)-sulfoximine [15985-39-4], induced convulsions in mice and inhibited glutamine synthetase [9023-70-5] irreversibly; α-ethylmethionine sulfoximine was .apprx.50% as inhibitory as methionine sulfoximine and α-methylmethionine sulfoximine. However, whereas α-methylmethionine sulfoximine and methionine sulfoximine inhibited γ-glutamylcysteine synthetase [9023-64-7] markedly, α-ethylmethionine sulfoximine did not, nor did administration of the α-Et analog produce the decrease in tissue glutathione [70-18-8] levels found after giving methionine sulfoximine or its α-Me analog. The α-alkyl methionine sulfoximine analogs cannot be catabolized via the corresponding α-keto or α-imino acids, and, like other α-substituted amino acids, are probably not metabolized to a significant extent in vivo; this suggests that the amino acid sulfoximine mols. themselves, rather than their metabolites, are directly involved in the induction of convulsions. Possible explanations for the reported lack of correlation between the occurrence of convulsions and the levels of glutamine synthetase activity (and its substrates and product) are considered.

SUPPL. TERM: alkyl methionine sulfoximine convulsion; methylmethionine sulfoximine convulsion; ethylmethionine sulfoximine convulsion; glutamine synthetase methionine sulfoximine; glutamylcysteine synthetase methionine sulfoximine
INDEX TERM: Convulsion
(from methionine sulfoximine, glutamine synthetase and glutamylcysteine synthetase in relation to)
INDEX TERM: Brain, composition
Kidney, composition
Liver, composition
(glutathione of, methionine sulfoximine effect on)
INDEX TERM: 15985-39-4 66735-68-0
ROLE: PRP (Properties)
(glutamine synthetase and glutamylcysteine synthetase inhibition by, convulsions in relation to)
INDEX TERM: 9023-70-5
ROLE: PRP (Properties)
(methionine sulfoximine analogs inhibition of, convulsions in relation to)

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INDEX TERM: 9023-64-7
ROLE: PRP (Properties)
(methionine sulfoximine inhibition of, convulsions in relation to)

INDEX TERM: 70-18-8, biological studies
ROLE: BIOL (Biological study)
(of organs, methionine sulfoximine effect on, convulsions in relation to)

INDEX TERM: 66735-67-9P
ROLE: PREP (Preparation)
(preparation and glutamine synthetase and glutamylcysteine synthetase inhibition by)

INDEX TERM: 66735-70-4P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrolysis of)

INDEX TERM: 66735-71-5P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation and sulfoximination of)

INDEX TERM: 66735-69-1P
ROLE: PREP (Preparation)
(preparation of)

INDEX TERM: 74-93-1, reactions
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with Et vinyl ketone)

INDEX TERM: 1629-58-9
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with Me mercaptan)

=> FIL HOME

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
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FILE 'HOME' ENTERED AT 13:01:43 ON 24 JUL 2006

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Last logoff:  24jul06 14:23:13
Logon file001 26jul06 12:02:06
          *** ANNOUNCEMENTS ***
                    ***
NEW FILES RELEASED
***EMCare (File 45)
***Trademarkscan - South Korea (File 655)
***Regulatory Affairs Journals (File 183)
***Index Chemicus (File 302)
***Inspec (File 202)

RESUMED UPDATING
***File 141, Reader's Guide Abstracts
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RELOADS COMPLETED
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***File 516, D&B--Dun's Market Identifiers
***File 523, D&B European Dun's Market Identifiers
***File 531, American Business Directory
*** The 2005 reload of the CLAIMS files (Files 340, 341, 942)
is now available online.
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***File 196, FINDEX
***File 468, Public Opinion Online (POLL)

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IMS R&D Focus (F445/955), Pharmaprojects (F128/928), Beilstein
Facts (F390), Derwent Chemistry Resource (F355) and Index Chemicus
(File 302).
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* * *

File   1:ERIC 1966-2006/June
       (c) format only 2006 Dialog

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Cost is in DialUnits
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            $0.40    0.114 DialUnits File1
     $0.40  Estimated cost File1
     $0.11  TELNET
     $0.51  Estimated cost this search
     $0.51  Estimated total session cost   0.114 DialUnits


SYSTEM:OS  - DIALOG OneSearch
  File   5:Biosis Previews(R) 1969-2006/Jul W3
         (c) 2006 The Thomson Corporation
  File  34:SciSearch(R) Cited Ref Sci 1990-2006/Jul W3
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? s glutamine()synthetase
           87595  GLUTAMINE
          109368  SYNTHETASE
      S2   19037  GLUTAMINE()SYNTHETASE
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      S3       0  ETHYL SULFOXIMINE
? s ethylmethionine sulfoximine
      S4       0  ETHYLMETHIONINE SULFOXIMINE
? s ethylmethionine()sulfoximine
              4  ETHYLMETHIONINE
          12353  SULFOXIMINE
      S5       4  ETHYLMETHIONINE()SULFOXIMINE
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      S6       3  RD  (unique items)
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6/5,K/1 (Item 1 from file: 5)

0002699570 BIOSIS NO.: 197968011069

INHIBITION OF GLUTATHIONE BIOSYNTHESIS BY PRO THIONINE SULFOXIMINE S-N PROPYL HOMO CYSTEINE SULFOXIMINE A SELECTIVE INHIBITOR OF GAMMA GLUTAMYL CYSTEINE SYNTHETASE

AUTHOR: GRIFFITH O W (Reprint); ANDERSON M E; MEISTER A
AUTHOR ADDRESS: DEP BIOCHEM, CORNELL UNIV MED COLL, NEW YORK, NY 10021, USA **USA

JOURNAL: Journal of Biological Chemistry 254 (4): p1205-1210 1979
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Methionine sulfoximine inhibits glutamine synthetase and .gamma.-glutamylcysteine synthetase by serving as an analog of the tetrahedral intermediate or transition state formed in the reaction of enzyme-bound .gamma.-glutamyl phosphate with ammonia or cysteine; injection of methionine sulfoximine into animals leads to decreased tissue levels of glutathione and glutamine. Previous studies showed that .alpha.- **ethylmethionine sulfoximine** inhibits glutamine synthetase but not .gamma.-glutamylcysteine synthetase. In the present studies, the reciprocal goal of inhibiting glutathione synthesis without substantially perturbing glutamine synthesis was apparently attained. Thus, prothionine sulfoximine, (S-n-propyl homocysteine sulfoximine) and .alpha.-methylprothionine sulfoximine were prepared and found to markedly inhibit .gamma.-glutamylcysteine synthetase but to not significantly affect glutamine synthetase. These sulfoximines are active in vivo and thus provide a useful experimental approach for selective inhibition of glutathione biosynthesis. After injection of prothionine sulfoximine into mice, the level of kidney glutathione decreased rapidly to about 20% of the control level, indicating that a large fraction, rather than a small

pool, of glutathione participates in rapid turnover. The rapid decline of the glutathione level that occurs after inhibition of glutathione synthesis reflects the normal rate of intracellular glutathione utilization by the .gamma.-glutamyl cycle. A number of related sulfoximines were synthesized and tested as inhibitors of glutamine and .gamma.-glutamylcysteine synthetases.

REGISTRY NUMBERS: 70-18-8: GLUTATHIONE; 14616-60-5: SULFOXIMINE; 9023-64-7: GAMMA-GLUTAMYLCYSTEINE SYNTHETASE; 9023-70-5: GLUTAMINE SYNTHETASE; 581-64-6: THIONINE
DESCRIPTORS: MOUSE METABOLIC-DRUG GLUTAMINE SYNTHETASE ALPHA ETHYL PRO THIONINE SULFOXIMINE GAMMA GLUTAMYL CYCLE
DESCRIPTORS:
MAJOR CONCEPTS: Enzymology--Biochemistry and Molecular Biophysics; Metabolism; Pharmacology; Urinary System--Chemical Coordination and Homeostasis
BIOSYSTEMATIC NAMES: Muridae--Rodentia, Mammalia, Vertebrata, Chordata, Animalia
COMMON TAXONOMIC TERMS: Animals; Chordates; Mammals; Nonhuman Vertebrates ; Nonhuman Mammals; Rodents; Vertebrates
CHEMICALS & BIOCHEMICALS: GLUTATHIONE; SULFOXIMINE; GAMMA-GLUTAMYLCYSTEINE SYNTHETASE; GLUTAMINE SYNTHETASE; THIONINE
CONCEPT CODES:
10010 Comparative biochemistry
10060 Biochemistry studies - General
10064 Biochemistry studies - Proteins, peptides and amino acids
10806 Enzymes - Chemical and physical
10808 Enzymes - Physiological studies
13002 Metabolism - General metabolism and metabolic pathways
13012 Metabolism - Proteins, peptides and amino acids
15504 Urinary system - Physiology and biochemistry
22003 Pharmacology - Drug metabolism and metabolic stimulators
22032 Pharmacology - Urinary system
22100 Routes of immunization, infection and therapy
BIOSYSTEMATIC CODES:
86375 Muridae

...ABSTRACT: animals leads to decreased tissue levels of glutathione and glutamine. Previous studies showed that .alpha.- **ethylmethionine sulfoximine** inhibits glutamine synthetase but not .gamma.-glutamylcysteine synthetase. In the present studies, the reciprocal goal...

6/5,K/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0002456730 BIOSIS NO.: 197866043214
DIFFERENTIAL INHIBITION OF GLUTAMINE AND GAMMA GLUTAMYL CYSTEINE SYNTHETASES BY ALPHA ALKYL ANALOGS OF METHIONINE SULFOXIMINE THAT INDUCE CONVULSIONS
AUTHOR: GRIFFITH O W (Reprint); MEISTER A
AUTHOR ADDRESS: DEP BIOCHEM, CORNELL UNIV MED COLL, NEW YORK, NY 10021, USA **USA
JOURNAL: Journal of Biological Chemistry 253 (7): p2333-2338 1978
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The .alpha.-methyl and .alpha.-ethyl analogs of methionine sulfoximine, like methionine sulfoximine, induce convulsions in mice and inhibit glutamine synthetase irreversibly; .alpha.- **ethylmethionine sulfoximine** is approximately 50% as inhibitory as methionine sulfoximine and .alpha.-methylmethionine sulfoximine. Whereas .alpha.-methylmethionine sulfoximine and methionine sulfoximine inhibit .gamma.-glutamylcysteine synthetase markedly, .alpha.- **ethylmethionine sulfoximine** does not, nor does administration of the .alpha.-ethyl analog produce the decrease in tissue glutathione levels found after giving methionine sulfoximine or its .alpha.-methyl analog. Methionine sulfoximine-induced convulsions may be closely associated with inhibition of glutamine synthetase rather than with inhibition of .gamma.-glutamylcysteine synthetase. The .alpha.-alkyl methionine sulfoximine analogs cannot be catabolized via the corresponding .alpha.-keto or .alpha.-imino acids, and, like other .alpha.-substituted amino acids, are probably not metabolized to a significant extent in vivo; this suggests that the amino acid sulfoximine molecules themselves, rather than their metabolites, are directly involved in the induction of convulsions. Possible explanations for the reported lack of correlation between the occurrence of convulsions and the levels of glutamine synthetase activity (and its substrates and product) are considered. Studies on the mechanism of induction of convulsions may be extended significantly and refined in biochemical terms by the use of other structurally modified convulsant molecules.

REGISTRY NUMBERS: 56-85-9Q: GLUTAMINE; 6899-04-3Q: GLUTAMINE; 9023-64-7D: GAMMA-GLUTAMYLCYSTEINE SYNTHETASES; 1982-67-8: METHIONINE SULFOXIMINE
DESCRIPTORS: MOUSE/
DESCRIPTORS:
MAJOR CONCEPTS: Enzymology--Biochemistry and Molecular Biophysics; Nervous System--Neural Coordination; Toxicology
BIOSYSTEMATIC NAMES: Muridae--Rodentia, Mammalia, Vertebrata, Chordata, Animalia
COMMON TAXONOMIC TERMS: Animals; Chordates; Mammals; Nonhuman Vertebrates ; Nonhuman Mammals; Rodents; Vertebrates
CHEMICALS & BIOCHEMICALS: GLUTAMINE; GLUTAMINE; GAMMA-GLUTAMYLCYSTEINE SYNTHETASES; METHIONINE SULFOXIMINE
CONCEPT CODES:
10010 Comparative biochemistry
10064 Biochemistry studies - Proteins, peptides and amino acids
10804 Enzymes - Methods
10808 Enzymes - Physiological studies
13012 Metabolism - Proteins, peptides and amino acids
20506 Nervous system - Pathology
22501 Toxicology - General and methods
BIOSYSTEMATIC CODES:
86375 Muridae

...ABSTRACT: methionine sulfoximine, like methionine sulfoximine, induce convulsions in mice and inhibit glutamine synthetase irreversibly; .alpha.- **ethylmethionine sulfoximine** is approximately 50% as inhibitory as methionine sulfoximine and .alpha.-methylmethionine sulfoximine. Whereas .alpha.-methylmethionine sulfoximine and methionine sulfoximine inhibit .gamma.-glutamylcysteine synthetase markedly, .alpha.- **ethylmethionine sulfoximine** does not, nor does administration of the .alpha.-ethyl analog produce the decrease in tissue...

6/5,K/3 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07458686 PMID: 3657547
Amino acid sulfoximines: alpha- ethylmethionine sulfoximine .
Griffith O W
Methods in enzymology (UNITED STATES) 1987, 143 p286-91, ISSN 0076-6879--Print Journal Code: 0212271
Contract/Grant No.: AM26912; AM; NIADDK
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS
Descriptors: *Methionine Sulfoximine--analogs and derivatives--AA; Chromatography, Ion Exchange; Indicators and Reagents; Methionine Sulfoximine--chemical synthesis--CS; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.; Stereoisomerism
CAS Registry No.: 0 (Indicators and Reagents); 1982-67-8 (Methionine Sulfoximine); 66735-68-0 (2-ethylmethionine sulfoximine)
Record Date Created: 19871030
Record Date Completed: 19871030
Amino acid sulfoximines: alpha- ethylmethionine sulfoximine .
Chemical Name: Indicators and Reagents; Methionine Sulfoximine; 2-**ethylmethionine sulfoximine**

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? s au=(griffith)
     S11        5  AU=(GRIFFITH)
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Set      Items   Description
S1        7288   GLUTAMINE SYNTHETASE
S2       19037   GLUTAMINE()SYNTHETASE
S3           0   ETHYL SULFOXIMINE
S4           0   -ETHYLMETHIONINE SULFOXIMINE
S5           4   ETHYLMETHIONINE()SULFOXIMINE
S6           3   RD  (unique items)
S7           5   AU=GRIFFITH
S8           0   AU=(GRIFFITH, O?)
S9           0   AU=(GRIFFITH, O?)
S10          4   AU=(GRIFFITH OWEN)
S11          5   AU=(GRIFFITH)
? s s11 and s2
                5  S11
            19037  S2
     S12        0  S11 AND S2
? s s11 and s5
                5  S11
                4  S5
     S13        0  S11 AND S5
? ds

Set      Items   Description
S1        7288   GLUTAMINE SYNTHETASE
S2       19037   GLUTAMINE()SYNTHETASE
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```
S3          0   ETHYL SULFOXIMINE
S4          0   ETHYLMETHIONINE SULFOXIMINE
S5          4   ETHYLMETHIONINE()SULFOXIMINE
S6          3   RD  (unique items)
S7          5   AU=GRIFFITH
S8          0   AU=(GRIFFITH, O?)
S9          0   AU=(GRIFFITH, O?)
S10         4   AU=(GRIFFITH OWEN)
S11         5   AU=(GRIFFITH)
S12         0   S11 AND S2
S13         0   S11 AND S5
? e griffith

Ref   Items  Index-term
E1       20  GRIFFISS
E2        2  GRIFFIT
E3     1790 *GRIFFITH
E4        1  GRIFFITH (AUSTRALIA) (AUSTRALASIAN REGION)
E5        2  GRIFFITH (NEW SOUTH WALES, AUSTRALIA) (AUSTRAL
E6        1  GRIFFITH AND STABILITY CRITERIA
E7        1  GRIFFITH ASSESSMENT SCALE
E8        2  GRIFFITH BROOK (VERMONT, USA, NORTH AMERICA) (
E9        1  GRIFFITH COLEMAN R
E10      34  GRIFFITH CRACK
E11       1  GRIFFITH CRACK PROBLEM
E12       2  GRIFFITH CRACK THEORY

          Enter P or PAGE for more
? p

Ref   Items  Index-term
E13       1  GRIFFITH CRACKING
E14       5  GRIFFITH CRACKS
E15      10  GRIFFITH CRITERION
E16       1  GRIFFITH D
E17       1  GRIFFITH DEVELOPMENTAL SCALE
E18       1  GRIFFITH E
E19       1  GRIFFITH E I
E20       1  GRIFFITH ENERGY BALANCE
E21       1  GRIFFITH FAILURE CRITERION
E22       1  GRIFFITH FLAWS
E23       1  GRIFFITH FORMULA
E24       1  GRIFFITH FRACTURE

          Enter P or PAGE for more
? p

Ref   Items  Index-term
E25       1  GRIFFITH FRED
E26       4  GRIFFITH G C
E27       1  GRIFFITH G H
E28       2  GRIFFITH H
E29       1  GRIFFITH H G
E30       8  GRIFFITH H R
E31       1  GRIFFITH HARBOUR (BRITISH COLUMBIA, CANADA, NO
E32       1  GRIFFITH HAROLD
E33       1  GRIFFITH HAROLD R
E34       1  GRIFFITH I
E35       1  GRIFFITH KENNETH M
E36       1  GRIFFITH LEAGE RANCH
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          Enter P or PAGE for more
? p

Ref    Items  Index-term
E37        1  GRIFFITH LEAGUE RANCH
E38        1  GRIFFITH LEAGUE RANCH, BASTROP COUNTY (TEXAS,
E39        2  GRIFFITH MENTAL DEVELOPMENT SCALE
E40        6  GRIFFITH MENTAL DEVELOPMENTAL SCALE
E41        1  GRIFFITH MENTAL DEVELOPMENTAL SCALE ASSESSMENT
E42        1  GRIFFITH METHOD
E43        1  GRIFFITH MODEL
E44        1  GRIFFITH NEW-SOUTH-WALES AUSTRALIA WIND CROP V
E45        1  GRIFFITH O
E46        1  GRIFFITH OWEN
E47        1  GRIFFITH P G
E48        1  GRIFFITH PROCEDURE

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? s e46
     S14       1 'GRIFFITH OWEN'
? t s15/3,k/1
>>>Set 15 does not exist
? t s14/3,k/1

 14/3,K/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2006 Dialog. All rts. reserv.

00325954   PMID: 14941727   Record Identifier: 5222-27875-193
  Owen Griffith; 1788-1865; country squire and medical manufacturer.
  JONES J G
  Practitioner (Not   Available)   May  1952,   168   (1007)   p520-2,  ISSN
0032-6518--Print   Journal Code: 0404245
  Publishing Model Print
  Document type: Biography; Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Other Citation Owner: CLML
  Record type: OLDMEDLINE; Completed

  Named Person:  GRIFFITH OWEN
? ds

Set     Items   Description
S1       7288   GLUTAMINE SYNTHETASE
S2      19037   GLUTAMINE()SYNTHETASE
S3          0   ETHYL SULFOXIMINE
S4          0   ETHYLMETHIONINE SULFOXIMINE
S5          4   ETHYLMETHIONINE()SULFOXIMINE
S6          3   RD  (unique items)
S7          5   AU=GRIFFITH
S8          0   AU=(GRIFFITH, O?)
S9          0   AU=(GRIFFITH, O?)
S10         4   AU=(GRIFFITH OWEN)
S11         5   AU=(GRIFFITH)
S12         0   S11 AND S2
S13         0   S11 AND S5
S14         1   'GRIFFITH OWEN'
? s ethylmethionine and sulfoximine
             4  ETHYLMETHIONINE
         12353  SULFOXIMINE
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     S15       4  ETHYLMETHIONINE AND SULFOXIMINE
? s ethyl methionine
     S16       0  ETHYL METHIONINE
? s ethyl()methionine
          193247  ETHYL
          130112  METHIONINE
     S17       8  ETHYL()METHIONINE
? s s17 and s2
               8  S17
           19037  S2
     S18       1  S17 AND S2
? t s18/5,k/all

 18/5,K/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2006 The Thomson Corporation. All rts. reserv.

0002788146   BIOSIS NO.: 198018027137
EFFECTS OF METHIONINE SULFOXIMINE ANALOGS ON THE SYNTHESIS OF L GLUTAMINE
  AND GLUTATHIONE POSSIBLE CHEMO THERAPEUTIC IMPLICATIONS
AUTHOR: MEISTER A (Reprint); GRIFFITH O W
AUTHOR ADDRESS: DEP BIOCHEM, CORNELL UNIV MED COLL, 1300 YORK AVE, NEW
  YORK, NY 10021, USA**USA
JOURNAL: Cancer Treatment Reports  63 (6): p1115-1121 1979
CONFERENCE/MEETING: WORKSHOP ON AMINO ACID IMBALANCE IN THE TREATMENT OF
CANCER, BETHESDA, MD., USA, MAY 23, 1978. CANCER TREAT REP.
ISSN: 0361-5960
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation
LANGUAGE: ENGLISH
REGISTRY NUMBERS: 1982-67-8: METHIONINE SULFOXIMINE; 56-85-9: L-GLUTAMINE;
    70-18-8: GLUTATHIONE; 14616-60-5: SULFOXIMINE; 9023-64-7:
    GAMMA-GLUTAMYLCYSTEINE SYNTHETASE; 9023-70-5: L- GLUTAMINE   SYNTHETASE

DESCRIPTORS: HUMAN MOUSE ALPHA ETHYL   METHIONINE  SULFOXIMINE PROTHIONINE
SULFOXIMINE ENZYME INHIBITOR-DRUG ANTINEOPLASTIC-DRUG SKIN CARCINOMA
CARCINOGENS L GAMMA GLUTAMYL CYSTEINE SYNTHETASE L  GLUTAMINE   SYNTHETASE
PHARMACODYNAMICS
DESCRIPTORS:
  MAJOR CONCEPTS: Enzymology--Biochemistry and Molecular Biophysics;
    Metabolism; Oncology--Human Medicine, Medical Sciences; Pharmacology
  BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata,
    Animalia; Muridae--Rodentia, Mammalia, Vertebrata, Chordata, Animalia
  COMMON TAXONOMIC TERMS: Humans; Primates; Animals; Chordates; Mammals;
    Nonhuman Vertebrates; Nonhuman Mammals; Rodents; Vertebrates
  CHEMICALS & BIOCHEMICALS:   METHIONINE SULFOXIMINE; L-GLUTAMINE;
    GLUTATHIONE; SULFOXIMINE; GAMMA-GLUTAMYLCYSTEINE SYNTHETASE; L-
    GLUTAMINE   SYNTHETASE
CONCEPT CODES:
  00520 General biology - Symposia, transactions and proceedings
  10060 Biochemistry studies - General
  10064 Biochemistry studies - Proteins, peptides and amino acids
  10808 Enzymes - Physiological studies
  12512 Pathology - Therapy
  13012 Metabolism - Proteins, peptides and amino acids
  18506 Integumentary system - Pathology
  22003 Pharmacology - Drug metabolism and metabolic stimulators
  22005 Pharmacology - Clinical pharmacology
  22020 Pharmacology - Integumentary system, dental and oral biology
  22501 Toxicology - General and methods
  24007 Neoplasms - Carcinogens and carcinogenesis
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  24008 Neoplasms - Therapeutic agents and therapy
  38502 Chemotherapy - General, methods and metabolism
BIOSYSTEMATIC CODES:
  86215 Hominidae
  86375 Muridae

...REGISTRY NUMBERS: L- GLUTAMINE   SYNTHETASE
DESCRIPTORS: HUMAN MOUSE ALPHA  ETHYL   METHIONINE  SULFOXIMINE PROTHIONINE
SULFOXIMINE ENZYME INHIBITOR-DRUG ANTINEOPLASTIC-DRUG SKIN CARCINOMA
CARCINOGENS L GAMMA GLUTAMYL CYSTEINE SYNTHETASE L  GLUTAMINE   SYNTHETASE
PHARMACODYNAMICS
DESCRIPTORS:
  CHEMICALS & BIOCHEMICALS:   ...L- GLUTAMINE   SYNTHETASE
? s au=(horwitz M?)
     S19     1365  AU=(HORWITZ M?)
? s s19 and glutamine
            1365  S19
           87595  GLUTAMINE
     S20       40  S19 AND GLUTAMINE
? s s20 and ethyl?
>>>File 5 processing for ETHYL? stopped at ETHYLGLUCURONOPYRANOSYL
>>>File 34 processing for ETHYL? stopped at ETHYLENEDITHIOTE
>>>File 155 processing for ETHYL? stopped at ETHYLNOREPHEDRINE
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          436853  ETHYL?
     S21       0  S20 AND ETHYL?
? s s20 and extracellular
              40  S20
          617621  EXTRACELLULAR
     S22      20  S20 AND EXTRACELLULAR
? ds

Set     Items   Description
S1       7288   GLUTAMINE SYNTHETASE
S2      19037   GLUTAMINE()SYNTHETASE
S3          0   ETHYL SULFOXIMINE
S4          0   ETHYLMETHIONINE SULFOXIMINE
S5          4   ETHYLMETHIONINE()SULFOXIMINE
S6          3   RD  (unique items)
S7          5   AU=GRIFFITH
S8          0   AU=(GRIFFITH, O?)
S9          0   AU=(GRIFFITH, O?)
S10         4   AU=(GRIFFITH OWEN)
S11         5   AU=(GRIFFITH)
S12         0   S11 AND S2
S13         0   S11 AND S5
S14         1   'GRIFFITH OWEN'
S15         4   ETHYLMETHIONINE AND SULFOXIMINE
S16         0   ETHYL METHIONINE
S17         8   ETHYL()METHIONINE
S18         1   S17 AND S2
S19      1365   AU=(HORWITZ M?)
S20        40   S19 AND GLUTAMINE
S21         0   S20 AND ETHYL?
S22        20   S20 AND EXTRACELLULAR
? s s20 and s2
              40  S20
           19037  S2
     S23      40  S20 AND S2
? s s20 and mycobacte?
              40  S20
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          187477  MYCOBACTE?
     S24       40  S20 AND MYCOBACTE?
? s s24 and cell()wall
              40  S24
         8044967  CELL
          527829  WALL
          104545  CELL(W)WALL
     S25       16  S24 AND CELL()WALL
? s s25 and glutamate
              16  S25
          258365  GLUTAMATE
     S26       12  S25 AND GLUTAMATE
? rd
     S27        5  RD  (unique items)
? t s27/5,k/all

 27/5,K/1      (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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0012384759   BIOSIS NO.: 200000103072
Treatment of Mycobacterium tuberculosis with antisense oligonucleotides
  to glutamine synthetase mRNA inhibits glutamine synthetase activity,
  formation of the poly-L- glutamate / glutamine cell wall structure,
  and bacterial replication
AUTHOR: Harth Gunter; Zamecnik Paul C; Tang Jin-Yan; Tabatadze David;
  Horwitz Marcus A (Reprint)
AUTHOR ADDRESS: Division of Infectious Diseases, Department of Medicine,
  School of Medicine, University of California, 10833 Le Conte Avenue,
  37-121 CHS, Los Angeles, CA, 90095, USA**USA
JOURNAL: Proceedings of the National Academy of Sciences of the United
States of America  97 (1): p418-423 Jan. 4, 2000 2000
MEDIUM: print
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: New antibiotics to combat the emerging pandemic of drug-resistant
  strains of Mycobacterium tuberculosis are urgently needed. We have
  investigated the effects on M. tuberculosis of phosphorothioate-modified
  antisense oligodeoxyribonucleotides (PS-ODNs) against the mRNA of
  glutamine synthetase, an enzyme whose export is associated with
  pathogenicity and with the formation of a poly-L- glutamate / glutamine
  cell wall structure. Treatment of virulent M. tuberculosis with 10 muM
  antisense PS-ODNs reduced glutamine synthetase activity and expression
  by 25-50% depending on whether one, two, or three different PS-ODNs were
  used and the PS-ODNs' specific target sites on the mRNA. Treatment with
  PS-ODNs of a recombinant strain of Mycobacterium smegmatis expressing
  M. tuberculosis glutamine synthetase selectively inhibited the
  recombinant enzyme but not the endogenous enzyme for which the mRNA
  transcript was mismatched by 2-4 nt. Treatment of M. tuberculosis with
  the antisense PS-ODNs also reduced the amount of poly-L- glutamate /
  glutamine in the cell wall by 24%. Finally, treatment with antisense
  PS-ODNs reduced M. tuberculosis growth by 0.7 logs (1 PS-ODN) to 1.25
  logs (3 PS-ODNs) but had no effect on the growth of M. smegmatis, which
  does not export glutamine synthetase nor possess the poly-L- glutamate
  / glutamine (P-L-glx) cell wall structure. The experiments indicate
  that the antisense PS-ODNs enter the cytoplasm of M. tuberculosis and
  bind to their cognate targets. Although more potent ODN technology is
```

needed, this study demonstrates the feasibility of using antisense ODNs in the antibiotic armamentarium against M. tuberculosis.
REGISTRY NUMBERS: 9023-70-5: **glutamine** synthetase
DESCRIPTORS:
MAJOR CONCEPTS: Biochemistry and Molecular Biophysics; Infection
BIOSYSTEMATIC NAMES: **Mycobacteriaceae** -- **Mycobacteria** , Actinomycetes and Related Organisms, Eubacteria, Bacteria, Microorganisms
ORGANISMS: **Mycobacterium** smegmatis (**Mycobacteriaceae**)--pathogen; **Mycobacterium** tuberculosis (**Mycobacteriaceae**)--pathogen, replication, virulent
COMMON TAXONOMIC TERMS: Bacteria; Eubacteria; Microorganisms
CHEMICALS & BIOCHEMICALS: **glutamine** synthetase--activity inhibition, expression; **glutamine** synthetase mRNA; mRNA; phosphorothioate-modified antisense oligodeoxyribonucleotides; poly-L-**glutamate** / **glutamine** -- **cell wall** structure formation
CONCEPT CODES:
10060 Biochemistry studies - General
10802 Enzymes - General and comparative studies: coenzymes
13002 Metabolism - General metabolism and metabolic pathways
30000 Bacteriology, general and systematic
36002 Medical and clinical microbiology - Bacteriology
38504 Chemotherapy - Antibacterial agents
BIOSYSTEMATIC CODES:
08881 **Mycobacteriaceae**
Treatment of Mycobacterium **tuberculosis with antisense oligonucleotides to** glutamine **synthetase mRNA inhibits** glutamine **synthetase activity, formation of the poly-L-** glutamate / glutamine cell wall **structure, and bacterial replication**
...AUTHOR: **Horwitz Marcus A**

ABSTRACT: New antibiotics to combat the emerging pandemic of drug-resistant strains of **Mycobacterium** tuberculosis are urgently needed. We have investigated the effects on M. tuberculosis of phosphorothioate-modified antisense oligodeoxyribonucleotides (PS-ODNs) against the mRNA of **glutamine** synthetase, an enzyme whose export is associated with pathogenicity and with the formation of a poly-L- **glutamate** / **glutamine** **cell wall** structure. Treatment of virulent M. tuberculosis with 10 muM antisense PS-ODNs reduced **glutamine** synthetase activity and expression by 25-50% depending on whether one, two, or three different...

...specific target sites on the mRNA. Treatment with PS-ODNs of a recombinant strain of **Mycobacterium** smegmatis expressing M. tuberculosis **glutamine** synthetase selectively inhibited the recombinant enzyme but not the endogenous enzyme for which the mRNA....

...of M. tuberculosis with the antisense PS-ODNs also reduced the amount of poly-L- **glutamate** / **glutamine** in the **cell wall** by 24%. Finally, treatment with antisense PS-ODNs reduced M. tuberculosis growth by 0.7...

...ODNs) but had no effect on the growth of M. smegmatis, which does not export **glutamine** synthetase nor possess the poly-L- **glutamate** / **glutamine** (P-L-glx) **cell wall** structure. The experiments indicate that the antisense PS-ODNs enter the cytoplasm of M. tuberculosis...
...REGISTRY NUMBERS: **glutamine** synthetase
DESCRIPTORS:
BIOSYSTEMATIC NAMES: **Mycobacteriaceae** --...

... **Mycobacteria** , Actinomycetes and Related Organisms, Eubacteria, Bacteria, Microorganisms
ORGANISMS: **Mycobacterium** smegmatis (**Mycobacteriaceae**)--...

... **Mycobacterium** tuberculosis (**Mycobacteriaceae**)--
CHEMICALS & BIOCHEMICALS: **glutamine** synthetase...

... **glutamine** synthetase mRNA...

...poly-L- **glutamate / glutamine** --...

... **cell wall** structure formation
BIOSYSTEMATIC CODES:
08881 **Mycobacteriaceae**

27/5,K/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012014555 BIOSIS NO.: 199900274215
An inhibitor of exported Mycobacterium **tuberculosis** glutamine **synthetase selectively blocks the growth of pathogenic** mycobacteria **in axenic culture and in human monocytes: Extracellular proteins as potential novel drug targets**
AUTHOR: Harth Gunter; **Horwitz Marcus A** (Reprint)
AUTHOR ADDRESS: Department of Medicine, 37-121 CHS, School of Medicine, University of California at Los Angeles, 10833 Le Conte Ave., Los Angeles, CA, 90095, USA**USA
JOURNAL: Journal of Experimental Medicine 189 (9): p1425-1435 May 3, 1999 1999
MEDIUM: print
ISSN: 0022-1007
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: **Mycobacterium** tuberculosis and other pathogenic **mycobacteria** export abundant quantities of proteins into their extracellular milieu when growing either axenically or within phagosomes of host cells. One major extracellular protein, the enzyme **glutamine** synthetase, is of particular interest because of its link to pathogenicity. Pathogenic **mycobacteria** , but not nonpathogenic **mycobacteria** , export large amounts of this protein. Interestingly, export of the enzyme is associated with the presence of a poly-L- **glutamate / glutamine** structure in the **mycobacterial cell wall** . In this study, we investigated the influence of **glutamine** synthetase inhibitors on the growth of pathogenic and nonpathogenic **mycobacteria** and on the poly-L- **glutamate / glutamine cell wall** structure. The inhibitor L-methionine-S-sulfoximine rapidly inactivated purified M. tuberculosis **glutamine** synthetase, which was 100-fold more sensitive to this inhibitor than a representative mammalian **glutamine** synthetase. Added to cultures of pathogenic **mycobacteria** , L-methionine-S-sulfoximine rapidly inhibited extracellular **glutamine** synthetase in a concentration-dependent manner but had only a minimal effect on cellular **glutamine** synthetase, a finding consistent with failure of the drug to cross the **mycobacterial cell wall** . Remarkably, the inhibitor selectively blocked the growth of pathogenic **mycobacteria** , all of which release **glutamine** synthetase extracellularly, but had no effect on nonpathogenic **mycobacteria** or nonmycobacterial microorganisms, none of which release **glutamine** synthetase extracellularly. The inhibitor was also bacteriostatic for M. tuberculosis in human mononuclear phagocytes (THP-1 cells), the pathogen's primary host cells. Paralleling and perhaps

underlying its bacteriostatic effect, the inhibitor markedly reduced the amount of poly-L- **glutamate / glutamine cell wall** structure in M. tuberculosis. Although it is possible that **glutamine** synthetase inhibitors interact with additional extracellular proteins or structures, our findings support the concept that extracellular proteins of M. tuberculosis and other pathogenic **mycobacteria** are worthy targets for new antibiotics. Such proteins constitute readily accessible targets of these relatively impermeable organisms, which are rapidly developing resistance to conventional antibiotics.

REGISTRY NUMBERS: 56-85-9Q: **glutamine** ; 6899-04-3Q: **glutamine** ; 9023-70-5: **glutamine** synthetase; 26700-71-0: poly-L- **glutamine**
DESCRIPTORS:
MAJOR CONCEPTS: Enzymology--Biochemistry and Molecular Biophysics; Immune System--Chemical Coordination and Homeostasis; Infection
BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia; **Mycobacteriaceae -- Mycobacteria** , Actinomycetes and Related Organisms, Eubacteria, Bacteria, Microorganisms
ORGANISMS: human (Hominidae); **Mycobacterium** tuberculosis (**Mycobacteriaceae**)--pathogen
ORGANISMS: PARTS ETC: monocyte--blood and lymphatics, immune system
COMMON TAXONOMIC TERMS: Animals; Chordates; Humans; Mammals; Primates; Vertebrates; Bacteria; Eubacteria; Microorganisms
DISEASES: tuberculosis--bacterial disease
MESH TERMS: Tuberculosis (MeSH)
CHEMICALS & BIOCHEMICALS: enzyme inhibitor; **glutamine** ; **glutamine** synthetase; poly-L- **glutamine**
MISCELLANEOUS TERMS: drug design
CONCEPT CODES:
34504 Immunology - Bacterial, viral and fungal
10808 Enzymes - Physiological studies
36002 Medical and clinical microbiology - Bacteriology
BIOSYSTEMATIC CODES:
86215 Hominidae
08881 **Mycobacteriaceae**

An inhibitor of exported Mycobacterium **tuberculosis** glutamine **synthetase selectively blocks the growth of pathogenic** mycobacteria **in axenic culture and in human monocytes: Extracellular proteins as potential novel drug targets**
...AUTHOR: **Horwitz Marcus A**

ABSTRACT: **Mycobacterium** tuberculosis and other pathogenic **mycobacteria** export abundant quantities of proteins into their extracellular milieu when growing either axenically or within phagosomes of host cells. One major extracellular protein, the enzyme **glutamine** synthetase, is of particular interest because of its link to pathogenicity. Pathogenic **mycobacteria** , but not nonpathogenic **mycobacteria** , export large amounts of this protein. Interestingly, export of the enzyme is associated with the presence of a poly-L- **glutamate / glutamine** structure in the **mycobacterial cell wall** . In this study, we investigated the influence of **glutamine** synthetase inhibitors on the growth of pathogenic and nonpathogenic **mycobacteria** and on the poly-L- **glutamate / glutamine cell wall** structure. The inhibitor L-methionine-S-sulfoximine rapidly inactivated purified M. tuberculosis **glutamine** synthetase, which was 100-fold more sensitive to this inhibitor than a representative mammalian **glutamine** synthetase. Added to cultures of pathogenic **mycobacteria** , L-methionine-S-sulfoximine rapidly inhibited extracellular **glutamine** synthetase in a concentration-dependent manner but had only a minimal effect on cellular

glutamine synthetase, a finding consistent with failure of the drug to cross the **mycobacterial cell wall** . Remarkably, the inhibitor selectively blocked the growth of pathogenic **mycobacteria** , all of which release **glutamine** synthetase extracellularly, but had no effect on nonpathogenic **mycobacteria** or nonmycobacterial microorganisms, none of which release **glutamine** synthetase extracellularly. The inhibitor was also bacteriostatic for M. tuberculosis in human mononuclear phagocytes (THP...

...and perhaps underlying its bacteriostatic effect, the inhibitor markedly reduced the amount of poly-L- **glutamate / glutamine cell wall** structure in M. tuberculosis. Although it is possible that **glutamine** synthetase inhibitors interact with additional extracellular proteins or structures, our findings support the concept that extracellular proteins of M. tuberculosis and other pathogenic **mycobacteria** are worthy targets for new antibiotics. Such proteins constitute readily accessible targets of these relatively...
...REGISTRY NUMBERS: **glutamine** ; ...

... **glutamine** ; ...

... **glutamine** synthetase...

...poly-L- **glutamine**
DESCRIPTORS:
...BIOSYSTEMATIC NAMES: **Mycobacteriaceae** --...

... **Mycobacteria** , Actinomycetes and Related Organisms, Eubacteria, Bacteria, Microorganisms
...ORGANISMS: **Mycobacterium** tuberculosis (**Mycobacteriaceae**)--
CHEMICALS & BIOCHEMICALS: ... **glutamine** ; ...

... **glutamine** synthetase...

...poly-L- **glutamine**
BIOSYSTEMATIC CODES:
...08881 **Mycobacteriaceae**

27/5,K/3 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

14498336 Genuine Article#: 978SR Number of References: 42
Title: All four Mycobacterium **tuberculosis glnA genes encode** glutamine **synthetase activities but only GlnA1 is abundantly expressed and essential for bacterial homeostasis**
Author(s): Harth G; Maslesa-Galic S; Tullius MV; **Horwitz MA (REPRINT)**
Corporate Source: Univ Calif Los Angeles,Sch Med, Dept Med, Div Infect Dis,37-121 CHS,10833 Le Conte Ave/Los Angeles//CA/90095 (REPRINT); Univ Calif Los Angeles,Sch Med, Dept Med, Div Infect Dis,Los Angeles//CA/90095(mhorwitz@mednet.ucla.edu)
Journal: MOLECULAR MICROBIOLOGY, 2005, V58, N4 (NOV), P1157-1172
ISSN: 0950-382X Publication date: 20051100
Publisher: BLACKWELL PUBLISHING, 9600 GARSINGTON RD, OXFORD OX4 2DQ, OXON, ENGLAND
Language: English Document Type: ARTICLE
Geographic Location: USA
Journal Subject Category: BIOCHEMISTRY & MOLECULAR BIOLOGY; MICROBIOLOGY
Abstract: **Glutamine** synthetases (GS) are ubiquitous enzymes that play a

central role in every cell's nitrogen metabolism. We have investigated the expression and activity of all four genomic **Mycobacterium** tuberculosis GS - GlnA1, GlnA2, GlnA3 and GlnA4 - and four enzymes regulating GS activity and/or nitrogen and **glutamate** metabolism - adenylyl transferase (GlnE), gamma-glutamylcysteine synthase (GshA), UDP-N-acetylmuramoylalanine-d- **glutamate** ligase (MurD) and **glutamate** racemase (MurI). All eight genes are located in multigene operons except for glnA1, and all are transcribed in M. tuberculosis; however, some are not translated or translated at such low levels that the enzymes escape detection. Of the four GS, only GlnA1 can be detected. Each of the eight genes, as well as the glnA1-glnE-glnA2 cluster, was expressed separately in **Mycobacterium** smegmatis, and its gene product was characterized and assayed for enzymatic activity by analysing the reaction products. In M. smegmatis, all four recombinant-overexpressed GS are multimeric enzymes exhibiting GS activity. Whereas GlnA1, GlnA3 and GlnA4 catalyse the synthesis of L- **glutamine** , GlnA2 catalyses the synthesis of D- **glutamine** and D-isoglutamine. The generation of mutants in M. tuberculosis of the four glnA genes, murD and murI demonstrated that all of these genes except glnA1 are nonessential for in vitro growth. L-methionine-S,R-sulphoximine (MSO), previously demonstrated to inhibit M. tuberculosis growth in vitro and in vivo, strongly inhibited all four GS enzymes; hence, the design of MSO analogues with an improved therapeutic to toxic ratio remains a promising strategy for the development of novel anti-M. tuberculosis drugs.

Identifiers--KeyWord Plus(R): COMPLETE GENOME SEQUENCE; ESCHERICHIA-COLI; SALMONELLA-TYPHIMURIUM; ALANINE RACEMASE; CORYNEBACTERIUM-GLUTAMICUM; NUCLEOTIDE-SEQUENCE; GLOBAL SURVEILLANCE; **CELL - WALL** ; INHIBITION; GROWTH

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Title: All four Mycobacterium **tuberculosis glnA genes encode** glutamine **synthetase activities but only GlnA1 is abundantly expressed and essential for bacterial homeostasis**

Author(s): Harth G; Maslesa-Galic S; Tullius MV; **Horwitz MA (REPRINT)**

Abstract: **Glutamine** synthetases (GS) are ubiquitous enzymes that play a central role in every cell's nitrogen metabolism. We have investigated the expression and activity of all four genomic **Mycobacterium** tuberculosis GS - GlnA1, GlnA2, GlnA3 and GlnA4 - and four enzymes regulating GS activity and/or nitrogen and **glutamate** metabolism - adenylyl transferase (GlnE), gamma-glutamylcysteine synthase (GshA), UDP-N-acetylmuramoylalanine-d- **glutamate** ligase (MurD) and **glutamate** racemase (MurI). All eight genes are located in multigene operons except for glnA1, and all...

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...Identifiers--COMPLETE GENOME SEQUENCE; ESCHERICHIA-COLI; SALMONELLA-TYPHIMURIUM; ALANINE RACEMASE; CORYNEBACTERIUM-GLUTAMICUM; NUCLEOTIDE-SEQUENCE; GLOBAL SURVEILLANCE; **CELL - WALL** ; INHIBITION; GROWTH

27/5,K/4 (Item 1 from file: 71)

DIALOG(R)File 71:ELSEVIER BIOBASE

00154835 94162427

Glutamine **synthetase of** Mycobacterium **tuberculosis: Extracellular release and characterization of its enzymatic activity**

Harth G.; Clemens D.L.; **Horwitz M.A.**
ADDRESS: G. Harth, Center for the Health Sciences, School of Medicine, University of California, 10833 Le Conte Avenue, Los Angeles, CA 90024, United States

Journal: Proceedings of the National Academy of Sciences of the United States of America, 91/20 (9342-9346), 1994, United States
PUBLICATION DATE: 19940000
CODEN: PNASA
ISSN: 0027-8424
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English

We have investigated the activity and extracellular release of **glutamine**

synthetase (L- **glutamate** :ammonia ligase (ADP-forming), EC 6.3.1.2) of **Mycobacterium** tuberculosis. The purified, homogeneous M. tuberculosis **glutamine** synthetase appears to consist of 12 most likely identical subunits of M(r) 58,000, arranged in two superimposed hexagons. In the catalysis of L- **glutamine** , the enzyme has an apparent K(m) for L- **glutamate** of approx. eq.3 mM at the pH optimum of 7.5. M. tuberculosis releases a large proportion (approx. eq.30%) of its total measurable enzyme activity into the culture medium, a feature that is highly specific for pathogenic **mycobacteria** . Immunogold electron microscopy revealed that M. tuberculosis also releases the enzyme into its phagosome in infected human monocytes. Two potentially important roles for **glutamine** synthetase in the pathogenesis of M. tuberculosis infection are (i) the synthesis of L- **glutamine** , a major component of the **cell wall** of pathogenic but not nonpathogenic **mycobacteria** , and (ii) the modulation of the ammonia level in the M. tuberculosis phagosome, which may in turn influence phagosomal pH and phagosome-lysosome fusion.

DESCRIPTORS:
tuberculosis; nitrogen metabolism; pathogenesis; ammonia regulation

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27/5,K/5 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14116641 PMID: 12496196
Inhibition of Mycobacterium **tuberculosis** glutamine **synthetase as a novel antibiotic strategy against tuberculosis: demonstration of efficacy in vivo.**
Harth Gunter; **Horwitz Marcus A**
Department of Medicine, School of Medicine, University of California, Los Angeles, California 90095-1688, USA.
Infection and immunity (United States) . Jan 2003, 71 . (1) p456-64, ISSN 0019-9567--Print Journal Code: 0246127
Contract/Grant No.: AI42925; AI; NIAID
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH

Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS; Toxbib

Tuberculosis remains one of humankind's greatest killers, and new therapeutic strategies are needed to combat the causative agent, **Mycobacterium** tuberculosis, which is rapidly developing resistance to conventional antibiotics. Using the highly demanding guinea pig model of pulmonary tuberculosis, we have investigated the feasibility of inhibiting M. tuberculosis **glutamine** synthetase (GS), an enzyme that plays a key role in both nitrogen metabolism and **cell wall** biosynthesis, as a novel antibiotic strategy. In guinea pigs challenged by aerosol with the highly virulent Erdman strain of M. tuberculosis, the GS inhibitor L-methionine-SR-sulfoximine (MSO) protected the animals against weight loss, a hallmark of tuberculosis, and against the growth of M. tuberculosis in the lungs and spleen; MSO reduced the CFU of M. tuberculosis at 10 weeks after challenge by approximately 0.7 log unit compared with that in control animals. MSO acted synergistically with isoniazid in protecting animals against weight loss and bacterial growth, reducing the CFU in the lungs and spleen by approximately 1.5 log units below the level seen with isoniazid alone. In the presence of ascorbate, which allows treatment with a higher dose, MSO was highly efficacious, reducing the CFU in the lungs and spleen by 2.5 log units compared with that in control animals. This study demonstrates that inhibition of M. tuberculosis GS is a feasible therapeutic strategy against this pathogen and supports the concept that M. tuberculosis enzymes involved in **cell wall** biosynthesis, including major secretory proteins, have potential as antibiotic targets.

Descriptors: *Anti-Bacterial Agents--therapeutic use--TU; *Antitubercular Agents--therapeutic use--TU; * **Glutamate** -Ammonia Ligase--antagonists and inhibitors--AI; *Methionine Sulfoximine--therapeutic use--TU; * **Mycobacterium** tuberculosis--drug effects--DE; *Tuberculosis, Pulmonary --drug therapy--DT; Animals; Anti-Bacterial Agents--pharmacology--PD; Antitubercular Agents--pharmacology--PD; Colony Count, Microbial; Disease Models, Animal; Drug Synergism; Guinea Pigs; Humans; Isoniazid--therapeutic use--TU; Lung--microbiology--MI; Methionine Sulfoximine--pharmacology--PD; Microbial Sensitivity Tests; **Mycobacterium** tuberculosis--enzymology--EN; Research Support, U.S. Gov't, P.H.S.; Spleen--microbiology--MI; Tuberculosis, Pulmonary--microbiology--MI

CAS Registry No.: 0 (Anti-Bacterial Agents); 0 (Antitubercular Agents) ; 1982-67-8 (Methionine Sulfoximine); 54-85-3 (Isoniazid)

Enzyme No.: EC 6.3.1.2 (**Glutamate** -Ammonia Ligase)

Record Date Created: 20021223

Record Date Completed: 20030210

Inhibition of Mycobacterium **tuberculosis** glutamine **synthetase as a novel antibiotic strategy against tuberculosis: demonstration of efficacy in vivo.**

Harth Gunter; **Horwitz Marcus A**

... humankind's greatest killers, and new therapeutic strategies are needed to combat the causative agent, **Mycobacterium** tuberculosis, which is rapidly developing resistance to conventional antibiotics. Using the highly demanding guinea pig model of pulmonary tuberculosis, we have investigated the feasibility of inhibiting M. tuberculosis **.glutamine** synthetase (GS), an enzyme that plays a key role in both nitrogen metabolism and **cell wall** biosynthesis, as a novel antibiotic strategy. In guinea pigs challenged by aerosol with the highly...

...therapeutic strategy against this pathogen and supports the concept that M. tuberculosis enzymes involved in **cell wall** biosynthesis, including major secretory proteins, have potential as antibiotic targets.

Descriptors: *Anti-Bacterial Agents--therapeutic use--TU; *Antitubercular

Agents--therapeutic use--TU; * **Glutamate** -Ammonia Ligase--antagonists and inhibitors--AI; *Methionine Sulfoximine--therapeutic use--TU; * **Mycobacterium** tuberculosis--drug effects--DE; *Tuberculosis, Pulmonary --drug therapy--DT...; Humans; Isoniazid--therapeutic use--TU; Lung --microbiology--MI; Methionine Sulfoximine--pharmacology--PD; Microbial Sensitivity Tests; **Mycobacterium** tuberculosis--enzymology--EN; Research Support, U.S. Gov't, P.H.S.; Spleen--microbiology--MI...
Enzyme No.: EC 6.3.1.2 (**Glutamate** -Ammonia Ligase)
Chemical Name: Anti-Bacterial Agents; Antitubercular Agents; Methionine Sulfoximine; Isoniazid; **Glutamate** -Ammonia Ligase

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Set     Items   Description
S1       7288   GLUTAMINE SYNTHETASE
S2      19037   GLUTAMINE()SYNTHETASE
S3          0   ETHYL SULFOXIMINE
S4          0   ETHYLMETHIONINE SULFOXIMINE
S5          4   ETHYLMETHIONINE()SULFOXIMINE
S6          3   RD  (unique items)
S7          5   AU=GRIFFITH
S8          0   AU=(GRIFFITH, O?)
S9          0   AU=(GRIFFITH, O?)
S10         4   AU=(GRIFFITH OWEN)
S11         5   AU=(GRIFFITH)
S12         0   S11 AND S2
S13         0   S11 AND S5
S14         1   'GRIFFITH OWEN'
S15         4   ETHYLMETHIONINE AND SULFOXIMINE
S16         0   ETHYL METHIONINE
S17         8   ETHYL()METHIONINE
S18         1   S17 AND S2
S19      1365   AU=(HORWITZ M?)
S20        40   S19 AND GLUTAMINE
S21         0   S20 AND ETHYL?
S22        20   S20 AND EXTRACELLULAR
S23        40   S20 AND S2
S24        40   S20 AND MYCOBACTE?
S25        16   S24 AND CELL()WALL
S26        12   S25 AND GLUTAMATE
S27         5   RD  (unique items)
? s au=(harth G?)
     S28     144  AU=(HARTH G?)
? s s28 and glutamine and glutamate
             144  S28
           87595  GLUTAMINE
          258365  GLUTAMATE
     S29      22  S28 AND GLUTAMINE AND GLUTAMATE
? s29 and mycobact?
          677127  29
          187520  MYCOBACT?
     S30    3290  29 AND MYCOBACT?
? s s29 and mycobact?
              22  S29
          187520  MYCOBACT?
     S31      22  S29 AND MYCOBACT?
? rd
     S32       9  RD  (unique items)
? s s32 not s27
               9  S32
               5  S27
     S33       6  S32 NOT S27
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>>>One or more prefixes are unsupported
>>>  or undefined in one or more files.
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          7107898  PD<2003
     S34        1  S33 AND PD<2003
? s s33 and py<2003
Processing
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         41701372  PY<2003
     S35        4  S33 AND PY<2003
? t s35/5,k/all
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35/5,K/1 (Item 1 from file: 5)

0009496539 BIOSIS NO.: 199497517824

Glutamine synthetase of Mycobacterium tuberculosis: Extracellular release and characterization of its enzymatic activity

AUTHOR: **Harth Gunter** (Reprint); Clemens Daniel L; Howritz Marcus A
AUTHOR ADDRESS: Div. Infectious Diseases, Dep. Med., 37-121 Center Health Sci., Sch. Med., University California, 10833 Le Conte Ave., Los Angeles, CA 90024, USA**USA

JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 91 (20): p9342-9346 1994 **1994**
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have investigated the activity and extracellular release of **glutamine** synthetase (L- **glutamate** :ammnonia ligase (ADP-forming), EC 6.3.1.2) of **Mycobacterium** tuberculosis. The purified, homogeneous M. tuberculosis **glutamine** synthetase appears to consist of 12 most likely identical subunits of M-r 58,000, arranged in two superimposed hexagons. In the catalysis of L- **glutamine** , the enzyme has an apparent K-m for L- **glutamate** of apprxeq 3 mM at the pH optimum of 7.5. M. tuberculosis releases a large proportion (apprxeq 30%) of its total measurable enzyme activity into the culture medium, a feature that is highly specific for pathogenic **mycobacteria** . Immunogold electron microscopy revealed that M. tuberculosis also releases the enzyme into its phagosome in infected human monocytes. Two potentially important roles for **glutamine** synthetase in the pathogenesis of M. tuberculosis infection are (i) the synthesis of L- **glutamine** , a major component of the cell wall of pathogenic but not nonpathogenic **mycobacteria** , and (ii) the modulation of the ammonia level in the M. tuberculosis phagosome, which may in turn influence phagosomal pH and phagosome-lysosome fusion.

REGISTRY NUMBERS: 9023-70-5: **GLUTAMINE**, SYNTHETASE; 9023-70-5: EC 6.3.1.2; 7727-37-9: NITROGEN; 7664-41-7: AMMONIA
DESCRIPTORS:
MAJOR CONCEPTS: Biochemistry and Molecular Biophysics; Enzymology--Biochemistry and Molecular Biophysics; Infection; Metabolism; Physiology
BIOSYSTEMATIC NAMES: **Mycobacteriaceae** -- **Mycobacteria** , Actinomycetes and Related Organisms, Eubacteria, Bacteria, Microorganisms
ORGANISMS: **Mycobacterium** tuberculosis (**Mycobacteriaceae**)

COMMON TAXONOMIC TERMS: Bacteria; Eubacteria; Microorganisms
CHEMICALS & BIOCHEMICALS: **GLUTAMINE** SYNTHETASE; EC 6.3.1.2; NITROGEN; AMMONIA
MISCELLANEOUS TERMS: AMMONIA REGULATION; EC 6.3.1.2; NITROGEN METABOLISM; PATHOGENESIS
CONCEPT CODES:
10060 Biochemistry studies - General
10064 Biochemistry studies - Proteins, peptides and amino acids
10506 Biophysics - Molecular properties and macromolecules
10806 Enzymes - Chemical and physical
10808 Enzymes - Physiological studies
13012 Metabolism - Proteins, peptides and amino acids
31000 Physiology and biochemistry of bacteria
36002 Medical and clinical microbiology - Bacteriology
BIOSYSTEMATIC CODES:
08881 **Mycobacteriaceae**

Glutamine **synthetase of** Mycobacterium **tuberculosis: Extracellular release and characterization of its enzymatic activity**
AUTHOR: **Harth Gunter** ...
1994

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...REGISTRY NUMBERS: **GLUTAMINE** - SYNTHETASE
DESCRIPTORS:
BIOSYSTEMATIC NAMES: **Mycobacteriaceae** --...

... **Mycobacteria** , Actinomycetes and Related Organisms, Eubacteria, Bacteria, Microorganisms
ORGANISMS: **Mycobacterium** tuberculosis (**Mycobacteriaceae**)
CHEMICALS & BIOCHEMICALS: **GLUTAMINE** SYNTHETASE...
BIOSYSTEMATIC CODES:
08881 **Mycobacteriaceae**

35/5,K/2 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06107565 Genuine Article#: XV492 Number of References: 21
Title: Expression and efficient export of enzymatically active Mycobacterium **tuberculosis** glutamine **synthetase in** Mycobacterium **smegmatis and evidence that the information for export is contained**

within the protein

Author(s): **Harth G** ; Horwitz MA (REPRINT)
Corporate Source: UNIV CALIF LOS ANGELES,SCH MED, DEPT MED, DIV INFECT DIS, 10833 LE CONTE AVE, 37-121 CHS/LOS ANGELES//CA/90095 (REPRINT); UNIV CALIF LOS ANGELES,SCH MED, DEPT MED, DIV INFECT DIS/LOS ANGELES//CA/90095

Journal: JOURNAL OF BIOLOGICAL CHEMISTRY, **1997** , V272, N36 (SEP 5), P 22728-22735
ISSN: 0021-9258 Publication date: 19970905
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814
Language: English Document Type: ARTICLE
Geographic Location: USA
Subfile: CC LIFE--Current Contents, Life Sciences
Journal Subject Category: BIOCHEMISTRY & MOLECULAR BIOLOGY

Abstract: We have investigated the expression and extracellular release of active, recombinant **Mycobacterium** tuberculosis **glutamine** synthetase (EC 6.3.1.2), an enzyme that is a potentially important determinant of M. tuberculosis infection and whose extracellular release is correlated with pathogenicity, The M. tuberculosis **glutamine** synthetase gene encodes a polypeptide of 478 amino acids; 12 such subunits comprise the active enzyme, Northern blot, nuclease S1, and primer extension analyses revealed **glutamine** synthetase specific transcripts of similar to 1,550 and 1,650 nucleotides produced under low and high nitrogen conditions, respectively, Expression of recombinant M. tuberculosis **glutamine** synthetase in Escherichia coli YMC21E, a **glutamine** synthetase deletion mutant, led to transcomplementation of the mutant but not to release of active enzyme, Expression in **Mycobacterium** smegmatis 1-2c, from the gene's own promoter, resulted in the release of > 95% of all recombinant enzyme, No hybrid molecules containing M. tuberculosis and M. smegmatis **glutam**ine synthetase subunits were detected, Native and recombinant exported and intracellular **glutamine** synthetase molecules were indistinguishable from one another by mass, N-terminal amino acid sequence, antibody reactivity, and enzymatic activity, Since M. tuberculosis **glutamine** synthetase is similar to other, strictly intracellular, bacterial **glutamine** synthetases and the DNA sequence upstream of the structural gene does not encode a leader peptide, the information to target the protein for export must be contained in its amino acid sequence and/or conformation.

Identifiers--KeyWord Plus(R): ESCHERICHIA-COLI; NUCLEOTIDE-SEQUENCE; GLNA; GENES; BACILLUS; REGION; LEPRAE
Research Fronts: 95-5061 001 (STRUCTURAL GENE; GLTC-DEPENDENT REGULATION OF BACILLUS-SUBTILIS **GLUTAMATE** SYNTHASE EXPRESSION; ARABIDOPSIS TYPE-1 PROTEIN PHOSPHATASE)

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REITZER LJ, 1985, V82, P1979, P NATL ACAD SCI USA
SANGER F, 1977, V74, P5463, P NATL ACAD SCI USA
THOLE JER, 1987, V55, P1466, INFECT IMMUN
WEISBROD RE, 1973, V248, P3997, J BIOL CHEM

Title: Expression and efficient export of enzymatically active Mycobacterium **tuberculosis** glutamine **synthetase in** Mycobacterium **smegmatis and evidence that the information** for export is contained **within the protein**

Author(s): **Harth G** ; Horwitz MA (REPRINT)

, **1997**

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Research Fronts: 95-5061 001 (STRUCTURAL GENE; GLTC-DEPENDENT REGULATION OF BACILLUS-SUBTILIS **GLUTAMATE** SYNTHASE EXPRESSION; ARABIDOPSIS TYPE-1 PROTEIN PHOSPHATASE)

35/5,K/3 (Item 1 from file: 155)

14033167 PMID: 12427974

Targeting the Mycobacterium **tuberculosis 30/32-kDa mycolyl transferase complex as a therapeutic strategy against tuberculosis: Proof of principle by using antisense technology.**

Harth Gunter ; Horwitz Marcus A; Tabatadze David; Zamecnik Paul C
Division of Infectious Diseases, Department of Medicine, 37-121 Center for Health Sciences, School of Medicine, University of California, 10833 Le Conte Avenue, Los Angeles 90095, USA.

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Contract/Grant No.: AI 42925; AI; NIAID
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Languages: ENGLISH
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We have investigated the effect of sequence-specific antisense phosphorothioate-modified oligodeoxyribonucleotides (PS-ODNs) targeting different regions of each of the 3032-kDa protein complex (antigen 85 complex) encoding genes on the multiplication of **Mycobacterium** tuberculosis. Single PS-ODNs to one of the three mycolyl transferase transcripts, added either once or weekly over the 6-wk observation period, inhibited bacterial growth by up to 1 log unit. A combination of three PS-ODNs specifically targeting all three transcripts inhibited bacterial growth by approximately 2 logs; the addition of these PS-ODNs weekly for 6 wk was somewhat more effective than a one-time addition. Targeting the 5' end of the transcripts was more inhibitory than targeting internal sites; the most effective PS-ODNs and target sites had minimal or no secondary structure. The effect of the PS-ODNs was specific, as mismatched PS-ODNs had little or no inhibitory activity. The antisense PS-ODNs, which were highly stable in M. tuberculosis cultures, specifically blocked protein expression by their gene target. PS-ODNs targeting the transcript of a related 24-kDa protein (mpt51) had little inhibitory effect by themselves and did not increase the effect of PS-ODNs against the three members of the 3032-kDa protein complex. The addition of PS-ODNs against the transcripts of **glutamine** synthetase I (glnA1) and alanine racemase (alr) modestly increased the inhibitory efficacy of the 3032-kDa protein complex-specific PS-ODNs to approximately 2.5 logs. This study shows that the three mycolyl transferases are highly promising targets for antituberculous therapy by using antisense or other antimicrobial technologies.

Descriptors: *Acyltransferases--drug effects--DE; *Antigens, Bacterial --drug effects--DE; *Bacterial Proteins--drug effects--DE; *Carrier Proteins--drug effects--DE; *Multienzyme Complexes--drug effects--DE; * **Mycobacterium** tuberculosis--drug effects--DE; *Oligodeoxyribonucleotides, Antisense--pharmacology--PD; *Thionucleotides--pharmacology--PD; *Tuberculosis--drug therapy--DT; Acyltransferases--biosynthesis--BI; Acyltransferases--genetics--GE; Acyltransferases--physiology--PH; Alanine Racemase--drug effects--DE; Alanine Racemase--genetics--GE; Antigens, Bacterial --biosynthesis--BI; Antigens, Bacterial--genetics--GE; Antigens, Bacterial--physiology--PH; Bacterial Proteins--biosynthesis--BI; Bacterial Proteins--genetics--GE; Bacterial Proteins--physiology--PH; Carrier Proteins--biosynthesis--BI; Carrier Proteins--genetics--GE; Carrier Proteins--physiology--PH; Cell Division--drug effects--DE; Drug Design; Drug Evaluation, Preclinical; Gene Expression Regulation, Bacterial--drug effects--DE; **Glutamate** -Ammonia Ligase--drug effects--DE; **Glutamate** -Ammonia Ligase--genetics--GE; Multienzyme Complexes--genetics--GE; **Mycobacterium** tuberculosis--enzymology--EN; **Mycobacterium** tuberculosis --growth and development--GD; Oligodeoxyribonucleotides, Antisense --chemistry--CH; RNA, Bacterial--antagonists and inhibitors--AI; RNA, Messenger--antagonists and inhibitors--AI; Research Support, Non-U.S. Gov't ; Research Support, U.S. Gov't, P.H.S.; Thionucleotides--chemistry--CH; Time Factors; Transcription, Genetic--drug effects--DE

CAS Registry No.: 0 (Antigens, Bacterial); 0 (Bacterial Proteins); 0 (Carrier Proteins); 0 (Multienzyme Complexes); 0 (Oligodeoxyribonucleotides, Antisense); 0 (RNA, Bacterial); 0 (RNA, Messenger); 0 (Thionucleotides)

Enzyme No.: EC 2.3. (Acyltransferases); EC 2.3.1.- (antigen 85A, **Mycobacterium** tuberculosis); EC 2.3.1.- (antigen 85B, **Mycobacterium** tuberculosis); EC 5.1.1.1 (Alanine Racemase); EC 6.3.1.- (glnA protein) ; EC 6.3.1.2 (**Glutamate** -Ammonia Ligase)

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Date of Electronic Publication: 20021111

Targeting the Mycobacterium **tuberculosis 30/32-kDa mycolyl transferase complex as a therapeutic strategy against tuberculosis: Proof of...**

Harth Gunter ; Horwitz Marcus A; Tabatadze David; Zamecnik Paul C

... **2002** ,

...of the 3032-kDa protein complex (antigen 85 complex) encoding genes on the multiplication of **Mycobacterium** tuberculosis. Single PS-ODNs to one of the three mycolyl transferase transcripts, added either once...

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...Descriptors: Bacterial Proteins--drug effects--DE; *Carrier Proteins --drug effects--DE; *Multienzyme Complexes--drug effects--DE; * **Mycobacterium** tuberculosis--drug effects--DE; *Oligodeoxyribonucleotides, Antisense--pharmacology--PD; *Thionucleotides--pharmacology--PD; *Tuberculosis--drug therapy--DT...; drug effects--DE; Drug Design; Drug Evaluation, Preclinical; Gene Expression Regulation, Bacterial--drug effects--DE; **Glutamate** -Ammonia Ligase--drug effects--DE; **Glutamate** -Ammonia Ligase --genetics--GE; Multienzyme Complexes--genetics--GE; **Mycobacterium** tuberculosis--enzymology--EN; **Mycobacterium** tuberculosis --growth and development--GD; Oligodeoxyribonucleotides, Antisense--chemistry--CH; RNA, Bacterial--antagonists and inhibitors--AI...

Enzyme No.: EC 2.3. (Acyltransferases); EC 2.3.1.- (antigen 85A, **Mycobacterium** tuberculosis); EC 2.3.1.- (antigen 85B, **Mycobacterium** tuberculosis); EC 5.1.1.1 (Alanine Racemase); EC 6.3.1.- (glnA protein) ; EC 6.3.1.2 (**Glutamate** -Ammonia Ligase)

...Chemical Name: Proteins; Carrier Proteins; Multienzyme Complexes; Oligodeoxyribonucleotides, Antisense; RNA, Bacterial; RNA, Messenger; Thionucleotides; Acyltransferases; antigen 85A, **Mycobacterium** tuberculosis; antigen 85B, **Mycobacterium** tuberculosis; Alanine Racemase; glnA protein; **Glutamate** -Ammonia Ligase

35/5,K/4 (Item 2 from file: 155)

13381165 PMID: 11553579

High extracellular levels of Mycobacterium **tuberculosis** glutamine **synthetase and superoxide dismutase in actively growing cultures are due to high expression and extracellular stability rather than to a protein-specific export mechanism.**

Tullius M V; **Harth G** ; Horwitz M A

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Infection and immunity (United States) Oct **2001** , 69 (10) p6348-63, ISSN 0019-9567--Print Journal Code: 0246127

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Glutamine synthetase (GS) and superoxide dismutase (SOD), large multimeric enzymes that are thought to play important roles in the pathogenicity of **Mycobacterium** tuberculosis, are among the bacterium's

major culture filtrate proteins in actively growing cultures. Although these proteins lack a leader peptide, their presence in the extracellular medium during early stages of growth suggested that they might be actively secreted. To understand their mechanism of export, we cloned the homologous genes (glnA1 and sodA) from the rapid-growing, nonpathogenic **Mycobacterium** smegmatis, generated glnA1 and sodA mutants of M. smegmatis by allelic exchange, and quantitated expression and export of both **mycobacterial** and nonmycobacterial GSs and SODs in these mutants. We also quantitated expression and export of homologous and heterologous SODs from M. tuberculosis. When each of the genes was expressed from a multicopy plasmid, M. smegmatis exported comparable proportions of both the M. tuberculosis and M. smegmatis GSs (in the glnA1 strain) or SODs (in the sodA strain), in contrast to previous observations in wild-type strains. Surprisingly, recombinant M. smegmatis and M. tuberculosis strains even exported nonmycobacterial SODs. To determine the extent to which export of these large, leaderless proteins is expression dependent, we constructed a recombinant M. tuberculosis strain expressing green fluorescent protein (GFP) at high levels and a recombinant M. smegmatis strain coexpressing the M. smegmatis GS, M. smegmatis SOD, and M. tuberculosis BfrB (bacterioferritin) at high levels. The recombinant M. tuberculosis strain exported GFP even in early stages of growth and at proportions very similar to those of the endogenous M. tuberculosis GS and SOD. Similarly, the recombinant M. smegmatis strain exported bacterioferritin, a large (approximately 500-kDa), leaderless, multimeric protein, in proportions comparable to GS and SOD. In contrast, high-level expression of the large, leaderless, multimeric protein malate dehydrogenase did not lead to extracellular accumulation because the protein was highly unstable extracellularly. These findings indicate that, contrary to expectations, export of M. tuberculosis GS and SOD in actively growing cultures is not due to a protein-specific export mechanism, but rather to bacterial leakage or autolysis, and that the extracellular abundance of these enzymes is simply due to their high level of expression and extracellular stability. The same determinants likely explain the presence of other leaderless proteins in the extracellular medium of actively growing M. tuberculosis cultures.

Descriptors: *Bacterial Proteins--metabolism--ME; * **Glutamate** -Ammonia Ligase--metabolism--ME; * **Mycobacterium** tuberculosis--enzymology--EN; *Superoxide Dismutase--metabolism--ME; Bacterial Proteins--genetics--GE; Biological Transport; Carbon--metabolism--ME; Culture Media; Cytochrome b Group--genetics--GE; Enzyme Stability; Ferritin--genetics--GE; Gene Expression; **Glutamate** -Ammonia Ligase--genetics--GE; Green Fluorescent Proteins; Luminescent Proteins--genetics--GE; Malate Dehydrogenase --biosynthesis--BI; **Mycobacterium** smegmatis--metabolism--ME; Nitrogen --metabolism--ME; Research Support, U.S. Gov't, P.H.S.; Superoxide Dismutase--genetics--GE

CAS Registry No.: 0 (Bacterial Proteins); 0 (Culture Media); 0 (Cytochrome b Group); 0 (Luminescent Proteins); 0 (SodA protein, Bacteria); 147336-22-9 (Green Fluorescent Proteins); 7440-44-0 (Carbon) ; 7727-37-9 (Nitrogen); 9007-73-2 (Ferritin); 9035-38-5 (bacterioferritin)

Enzyme No.: EC 1.1.1.37 (Malate Dehydrogenase); EC 1.15.1.1 (Superoxide Dismutase); EC 6.3.1.- (glnA protein); EC 6.3.1.2 (**G**lutamate -Ammonia Ligase)

Record Date Created: 20010912

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High extracellular levels of Mycobacterium **tuberculosis** glutamine **synthetase and superoxide dismutase in actively growing cultures are due to high expression and extracellular...**

Tullius M V; **Harth G** ; Horwitz M A

... 2001 ,
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Descriptors: *Bacterial Proteins--metabolism--ME; * **Glutamate** -Ammonia Ligase--metabolism--ME; * **Mycobacterium** tuberculosis--enzymology--EN; *Superoxide Dismutase--metabolism--ME...; ME; Culture Media; Cytochrome b Group--genetics--GE; Enzyme Stability; Ferritin--genetics--GE; Gene Expression; **Glutamate** -Ammonia Ligase--genetics--GE; Green Fluorescent Proteins; Luminescent Proteins--genetics--GE; Malate Dehydrogenase --biosynthesis--BI; **Mycobacterium** smegmatis--metabolism--ME; Nitrogen --metabolism--ME; Research Support, U.S. Gov't, P.H.S...
...Enzyme No.: 1.1 (Superoxide Dismutase); EC 6.3.1.- (glnA protein); EC 6.3.1.2 (**Glutamate** -Ammonia Ligase)
...Chemical Name: protein, Bacteria; Green Fluorescent Proteins; Carbon; Nitrogen; Ferritin; bacterioferritin; Malate Dehydrogenase; Superoxide Dismutase; glnA protein; **Glutamate** -Ammonia Ligase
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$126.69 Estimated cost this search
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